



## Original Article

## Current state of drug analysis in Japanese emergency departments: a nationwide survey

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**Aim:** In 1999, the Japanese Society for Clinical Toxicology proposed 15 toxicants that would be useful for analysis: methanol, barbiturates, benzodiazepines, bromovalerylurea, tricyclic acid, acetaminophen, salicylic acid, theophylline, organic phosphorus pesticides, carbamate pesticides, glufosinate, paraquat, arsenic, cyanide, and methamphetamine. We aimed to reveal the current state of drug analysis for acute poisoning in the emergency department of Japanese hospitals.

**Methods:** From 1 April, 2017, we undertook a questionnaire survey in the emergency departments of 546 hospitals designated as educational institutions for emergency physicians.

**Results:** Responses were obtained from 246 hospitals (45.1%). Among drug abuse screening kits for qualitative testing, 80.9% used the Triage Drugs of Abuse Panel and 7.3% used Instant-View M-1. Analytical results have always been immediately obtained by 2.8% of facilities for methanol, 19.5% for barbiturates, 2.4% for benzodiazepines, 0.8% for bromovalerylurea, 1.2% for tricyclic acid, 12.2% for acetaminophen, 4.1% for salicylic acid, 44.3% for theophylline, 2.0% for organic phosphorus pesticides, 1.6% for carbamate pesticides, 1.2% for glufosinate, 2.4% for paraquat, 0.8% for arsenic, 1.2% for cyanide, and 1.2% for methamphetamine.

**Conclusion:** In the treatment of acute poisoning, drug analysis is important for both clinical judgment and academic verification. However, many of the 15 toxicants proposed to be useful for analysis in 1999 are not yet immediately analyzed in the emergency department of Japanese hospitals. Furthermore, it is necessary to develop inexpensive testing systems and to provide insurance points for testing so that analysis can be carried out by emergency departments.

**Key words:** Emergency department, hospital laboratory, Japan, poisoning, toxicity test

## INTRODUCTION

IN CLINICAL TOXICOLOGY, measurement of the blood concentration of toxicants is useful for creation of a treatment plan and academic validation.

All authors are members of the Japanese Society for Clinical Toxicology, Case Study and Research Committee.

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In 1999, the Japanese Society for Clinical Toxicology published a list of toxicants useful for analysis based on the following three factors: (i) high mortality, (ii) direct clinical relevance of analysis, (iii) frequency of request for analysis by clinicians at that time. It was recommended that emergency care facilities be capable of testing for 15 of those toxicants, to maximize the utility of analytical instruments in routine clinical toxicology.<sup>1</sup>

However, only research institutions and some emergency and critical care centers have measurement systems such as mass spectrometers and are able to utilize the analysis results in patient care. Furthermore, many emergency care facilities, which are truly on the front line of clinical toxicology, lack the infrastructure for such testing. No study to date has determined to what extent Japanese emergency care facilities can undertake toxicological analyses.

This study assessed the current state of infrastructure for measurement of the blood concentration of toxicants in Japanese emergency care facilities.

This research was approved by the Ethics Committee of St. Luke's International Hospital, Tokyo, Japan (18-R095), and conforms to the provisions of the Declaration of Helsinki (as revised in 2013).

## METHODS

### Study design

**O**BSERVATIONAL STUDY USING a questionnaire.

### Subjects

The subjects were the emergency departments of 546 Japanese hospitals that were either a hospital designated by the JAAM for emergency physician education or had an Emergency Medical Service Center as of 1 April, 2017. No specific exclusion criteria were applied.

### Methods

Questionnaires were sent to directors at each facility and returned by mail.

### Data collected

- Facility background: Type of emergency care facility, employment status of emergency doctors, specialty of doctor in charge of managing patients with acute poisoning, appointment and specialty of toxicological analyst.
- Measurement of blood concentrations of toxicants (1): Infrastructure for measurement of blood concentrations of the 15 toxicants recommended as useful for analysis by the Japanese Society for Clinical Toxicology: (i) methanol, (ii) barbiturates, (iii) benzodiazepines, (iv) bromovalerylurea, (v) tricyclic acid, (vi) acetaminophen, (vii) salicylic acid, (viii) theophylline, (ix) organic phosphorus pesticides, (x) carbamate pesticides, (xi) glufosinate, (xii) paraquat, (xiii) arsenic, (xiv) cyanide, (xv) methamphetamine.
- Measurement of blood concentrations of toxicants (2): Infrastructure for measurement of blood concentrations of 5 other toxicants now considered potentially useful for analysis (i) caffeine, (ii) ethanol, (iii) lithium, (iv) ethylene glycol, (v) diphenhydramine.
- Use of screening kits for drugs of abuse.

### Data analysis

Collected results were entered into a database and analyzed using descriptive statistics.

## RESULTS

### Background

**R**ESPONSES TO THE questionnaire were obtained from 246 institutions (response rate, 45.1%). Ninety-five of these were secondary emergency care facilities, and 151 were tertiary emergency care facilities. In the Japanese emergency medical care system, secondary emergency care facilities are responsible for treating moderately sick patients who require hospital admission, whereas tertiary emergency care facilities are responsible for treating patients in critical condition, whose lives could be at risk.

Most hospitals appointed an emergency physician as the main staff member in charge of clinical toxicology, both inpatient and outpatient. The next most common specialty was internal medicine.

Only 65 facilities (26.4%) specifically appointed a staff member as a toxicological analyst. Forty-two of these appointed a clinical laboratory technician, 15 a pharmacist, and 5 a medical doctor (Table 1).

Twenty-two facilities (2 secondary and 20 tertiary emergency care facilities) used mass spectrometry to measure blood concentrations of toxicants in poisoned patients.

### Urine drug screening kits

The screening kits for drugs of abuse used for qualitative testing for poisoning were the Triage DOA Drugs of Abuse Panel (Sysmex, Kobe, Japan; 199 facilities, 80.9%) and Instant-View M-1 (name changed to IVEX-screen; Bio Design, Tokyo, Japan; 18 facilities, 7.3%). Some facilities used both kits. Twenty-four facilities (9.8%) did not use any screening kits.

### Infrastructure for measurement of blood concentrations of toxicants

Table 2 shows detailed results on infrastructure for measurement of blood concentrations of toxicants.

Facilities were assigned categories based on their ability to measure blood concentrations of the 15 toxicants recommended as useful for analysis by the Japanese Society for Clinical Toxicology and the five other new toxicants considered useful for analysis. A facility was marked as having Category I testing infrastructure for a given toxicant if it was

**Table 1.** Background of Japanese medical institutions that responded to a questionnaire survey regarding drug analysis for acute poisoning in emergency departments

		(n)	(n)
Type of emergency medical institution	Secondary emergency medical institution	95	
	Tertiary emergency medical institution	151	
	Advanced emergency medical service center		22
	Emergency medical service center		129
Designated hospital by JAAM <sup>†</sup>	Yes	241	
	No	5	
Full-time doctors enrolled in the emergency department	Yes	229	
	No	17	
Specialty of doctor in charge of patients with acute poisoning: outpatients (includes duplicate answers)	Emergency Medicine	221	
	Internal Medicine	46	
	Others	5	
	Various	5	
	Patients with poisoning not accepted	2	
Specialty of doctor in charge of patients with acute poisoning: inpatients (includes duplicate answers)	Emergency Medicine	181	
	Internal Medicine	70	
	Anesthesiology	3	
	Intensive care	3	
	Others	6	
	Patients with poisoning not accepted	3	
Appointment of a toxicological analyst	Yes	65	
	Doctor		5
	Clinical laboratory technician		42
	Pharmacist		15
	Others		3
	No	181	

Survey responses were received from 246 hospitals (46.5% response rate). Hospital background data are presented.

<sup>†</sup>The Japanese Association for Acute Medicine (JAAM) has designated certain hospitals for emergency physician education.

capable of urgent in-house testing for that toxicant (results always available within a few hours, including after hours), Category II if it was capable of in-house testing for that toxicant (same-day results), Category III if it was capable of sending specimens to an outside laboratory for testing, Category IV if it was capable of testing but did not do for some reason (e.g., cost of analysis), and Category V if it was not capable of testing.

Facilities must be Category I or II in order to utilize blood concentration measurements in emergency patient care. However, only a small percentage of facilities were capable of such testing. Toxicants tested through the general therapeutic drug monitoring system were barbiturates (I, 19.5%; II, 11.8%), theophylline (I, 44.3%; II, 18.3%), and lithium

(I, 11.4%; II, 11.4%), and toxicants tested solely for clinical toxicology were acetaminophen (I, 12.2%; II, 6.1%) and ethanol (I, 22.4%; II, 4.5%). Almost no facilities could utilize testing results for any other toxicants in emergency care.

Table 2 shows a breakdown of results for secondary and tertiary emergency care facilities. These results show that most facilities that have measurement infrastructure are tertiary emergency care facilities.

## Comments from responding facilities

Opinions about blood concentration measurement in patients with drug poisoning were shared by the facilities as comments on the questionnaire.

**Table 2.** Drug analysis environment in Japanese emergency departments

ID	Drug	Category of analysis environment					N/A
		I	II	III	IV	V	
1	Methanol	7 (2.8) 2 (2.1)	1 (0.4) 0 (0.0)	87 (35.4) 36 (37.9)	6 (2.4) 2 (2.1)	128 (52.0) 49 (51.6)	17 (6.9) 6 (6.3)
2	Barbiturate	48 (19.5) 17 (17.9)	29 (11.8) 8 (8.4)	60 (24.4) 30 (31.6)	5 (2.0) 0 (0.0)	77 (31.3) 33 (34.7)	27 (11.0) 7 (7.4)
3	Benzodiazepines	6 (2.4) 3 (3.2)	7 (2.8) 2 (2.1)	95 (38.6) 42 (44.2)	8 (3.3) 1 (1.1)	100 (40.7) 39 (41.1)	30 (12.2) 8 (8.4)
4	Bromovalerylurea	2 (0.8) 0 (0.0)	3 (1.2) 0 (0.0)	32 (13.0) 14 (14.7)	7 (2.8) 2 (2.1)	178 (72.4) 69 (72.6)	24 (9.8) 10 (10.5)
5	Tricyclic acid	3 (1.2) 0 (0.0)	6 (2.4) 0 (0.0)	60 (24.4) 29 (30.5)	8 (3.3) 2 (2.1)	140 (56.9) 56 (58.9)	29 (11.8) 8 (8.4)
6	Acetaminophen	30 (12.2) 3 (3.2)	15 (6.1) 2 (2.1)	141 (57.3) 62 (65.3)	3 (1.2) 0 (0.0)	51 (20.7) 25 (26.3)	6 (2.4) 3 (3.2)
7	Salicylic acid	10 (4.1) 1 (1.1)	9 (3.7) 1 (1.1)	147 (59.8) 59 (62.1)	8 (3.3) 2 (2.1)	60 (24.4) 26 (27.4)	12 (4.9) 6 (6.3)
8	Theophylline	109 (44.3) 33 (34.7)	45 (18.3) 14 (14.7)	59 (24.0) 33 (34.7)	2 (0.8) 0 (0.0)	23 (9.3) 10 (10.5)	8 (3.3) 5 (5.3)
9	Organic phosphorus pesticides	5 (2.0) 2 (2.1)	5 (2.0) 0 (0.0)	61 (24.8) 25 (26.3)	8 (3.3) 2 (2.1)	143 (58.1) 57 (60.0)	24 (9.8) 9 (9.5)
10	Carbamate pesticides	4 (1.6) 1 (1.1)	4 (1.6) 0 (0.0)	58 (23.6) 27 (28.4)	8 (3.3) 2 (2.1)	150 (61.0) 56 (58.9)	22 (8.9) 9 (9.5)
11	Glufosinate	3 (1.2) 0 (0.0)	6 (2.4) 0 (0.0)	24 (9.8) 12 (12.6)	5 (2.0) 1 (1.1)	187 (76.0) 72 (75.8)	21 (8.5) 10 (10.5)
12	Paraquat	6 (2.4) 1 (1.1)	5 (2.0) 0 (0.0)	70 (28.5) 30 (31.6)	5 (2.0) 1 (1.1)	137 (55.7) 55 (57.9)	23 (9.3) 8 (8.4)
13	Arsenic	2 (0.8) 0 (0.0)	4 (1.6) 0 (0.0)	50 (20.3) 21 (22.1)	4 (1.6) 1 (1.1)	167 (67.9) 64 (67.4)	19 (7.7) 9 (9.5)
14	Cyanide	3 (1.2) 0 (0.0)	3 (1.2) 0 (0.0)	24 (9.8) 12 (12.6)	6 (2.4) 1 (1.1)	189 (76.8) 72 (75.8)	21 (8.5) 10 (10.5)
15	Methamphetamine	3 (1.2) 1 (1.1)	3 (1.2) 0 (0.0)	40 (16.3) 18 (18.9)	4 (1.6) 1 (1.1)	168 (68.3) 64 (67.4)	28 (11.4) 11 (11.6)
16	Caffeine	3 (1.2) 0 (0.0)	5 (2.0) 0 (0.0)	43 (17.5) 17 (17.9)	8 (3.3) 3 (3.2)	164 (66.7) 67 (70.5)	23 (9.3) 8 (8.4)
17	Ethanol	55 (22.4) 9 (9.5)	11 (4.5) 0 (0.0)	105 (42.7) 51 (53.7)	5 (2.0) 4 (4.2)	60 (24.4) 28 (29.5)	10 (4.1) 3 (3.2)
18	Lithium	28 (11.4) 5 (5.3)	28 (11.4) 7 (7.4)	133 (54.1) 58 (61.1)	5 (2.0) 3 (3.2)	41 (16.7) 17 (17.9)	11 (4.5) 5 (5.3)

**Table 2.** (Continued)

ID	Drug	Category of analysis environment				
		I	II	III	IV	V
19	Ethylene glycol	<b>3 (1.2)</b> 0 (0.0)	<b>2 (0.8)</b> 0 (0.0)	<b>54 (22.0)</b> 24 (25.3)	<b>7 (2.8)</b> 2 (2.1)	<b>159 (64.6)</b> 59 (62.1)
20	Diphenhydramine	<b>4 (1.6)</b> 0 (0.0)	<b>4 (1.6)</b> 0 (0.0)	<b>30 (12.2)</b> 15 (15.8)	<b>8 (3.3)</b> 2 (2.1)	<b>174 (70.7)</b> 66 (69.5)

Data are shown as number (%). For each toxicant, bold values indicate the total number of institutions that analyze that toxicant. Immediately below, the values on the left indicate the number of secondary emergency medical institutions, and the values on the right indicate the number of tertiary emergency medical institutions. Analysis environment is defined according to five categories: **I**, results of analysis can always be acquired within a few hours, including after hours; **II**, results of analysis can be obtained on the same day; **III**, analysis needs to be commissioned to an external facility; **IV**, analysis is possible at own facility but not done; **V**, cannot analyze; N/A, no answer. Identifiers (ID) 1–15: toxicants recommended for analysis by the Japanese Society for Clinical Toxicology in 1999; 16–20, additional drugs investigated in the survey.

### Facilities must be compensated for their costs

- They want national health insurance to grant a fee for medical services for screening kits.
- They cannot introduce infrequently used testing systems due to depreciation costs.
- They are fully aware that blood concentration measurement is necessary, but it is not feasible at small- to medium-sized facilities (secondary emergency care facilities) from a cost perspective.

### Facilities want greater availability of screening kits

- They want increased availability of qualitative kits for toxicants such as methanol, arsenic, caffeine, organophosphates, salicylic acid, and acetaminophen.

### Facilities would like consolidation and systematization of blood concentration measurement

- They want centralized care for poisoned patients.
- They think it would be good to have a public facility that would readily accept specimens for blood concentration measurement.

## DISCUSSION

### Usefulness of measurement of blood concentrations of toxicants

WHEN CARING FOR patients with acute drug poisoning, measurement of the blood concentration of toxicants is important not only for clinical decision-making but also for academic validation.

Clinical symptoms obviously serve as the key evidence for determining whether special treatments are indicated for acute drug poisoning, but the blood concentration of the toxicant is a very useful indicator for early intervention to prevent fatal clinical symptoms before they develop.

One example of a special treatment for patients with drug poisoning is blood purification therapy. Guidelines state that the blood concentration of the toxicant should be reported as part of the standard format for case reports on the clinical effectiveness of blood purification therapy.<sup>2</sup>

It is recommended that criteria for starting special treatments, not only blood purification therapy but also others such as treatment with antagonists, be determined through academic validation based on past cases. Blood

concentration was used as reference data in many case reports from Europe and the USA.

### Infrastructure for toxicological analysis in Japan and past surveys on the state of that infrastructure

There were efforts to develop Japan's infrastructure for toxicological analysis in response to the Wakayama curry poisoning incident of 25 July, 1998, in which four people died and 63 fell ill after eating curry deliberately mixed with arsenic at a summer festival in Wakayama. The Japanese Ministry of Health equipped a total of 73 facilities (eight advanced emergency medical service centers and 65 emergency medical service centers) throughout Japan with analytical instruments to identify substances that cause poisoning as part of a government program.

In the present survey, almost all of the 20 tertiary emergency care facilities among the 22 facilities that reported using a mass spectrometer to measure blood concentrations of toxicants had received instruments from the government.

However, considering that clinical toxicology services are available at other facilities in addition to those few with advanced analytical instruments, this survey was carried out with 546 hospitals that were designated by the JAAM for emergency physician education or had an Emergency Medical Service Center in order to more faithfully represent the actual landscape of treatment for poisoned patients in Japan.

A total of 246 facilities, of which 95 were secondary emergency care facilities and 151 were tertiary emergency care facilities, responded to this survey. Their responses can be considered to more clearly reflect the actual situation at emergency care facilities, which are the main organizations involved in treating patients with drug poisoning.

### Infrastructure for measurement of blood concentrations of toxicants

Toxicological analysis should not be used indiscriminately to screen all patients with poisoning who have unclear symptoms, but rather should be applied diagnostically, focusing on particular toxicants.<sup>3,4</sup> To ensure toxicology results are useful in clinical decision-making, they must be quickly obtainable.

Toxicology guidelines from the UK and the USA, similar to those from Japan, list toxicants they recommend facilities be capable of testing. Both sets of guidelines separate these toxicants into those recommended for stat testing at medical facilities for prompt utilization of results of blood concentration analysis in clinical decision-making, and those that may be later analyzed at a specialist institution. The advised

turnaround time for stat testing for toxicants is within 2 h according to the UK guidelines and within 1 h according to the US guidelines.<sup>5,6</sup>

For test results to be utilized in clinical decision-making in a real-life emergency medicine setting, the turnaround time should ideally be immediate as an urgent test, or at latest on the same day the specimen was submitted for testing. In this survey, facilities with immediate results were labeled as Category I for measurement infrastructure, and facilities with same-day results as Category II.

Ideally, emergency care facilities on the front line of care for poisoned patients would have Category I measurement infrastructure for the recommended toxicants.

This survey revealed that many emergency care facilities are still not fully capable of testing for the 15 toxicants recommended as useful for analysis in 1999. Secondary emergency care facilities, in particular, lack the infrastructure for blood concentration measurement.

The situation around infrastructure for toxicological analysis is different in other countries. Data on the availability of toxicological analysis for the toxicants listed in the US recommendations were published in Ireland in 2008. Rapid analysis was most widely available for acetaminophen (74.4% of all hospitals that provided clinical toxicology services), and least widely available for methanol (2.6%).<sup>7</sup>

Comparison of the Japanese results from the present survey with these Irish results indicates that Japan's analytical infrastructure is well behind.

### Recommended toxicants

Twenty years have passed since the Japanese Society for Clinical Toxicology issued their list of 15 toxicants recommended for analysis. Since then, similar recommendations have been published in the USA (in 2003) and UK (in 2014). Table 3 compares the toxicants these guidelines recommend for immediate analysis, particularly at emergency care facilities.

This survey covered an additional five toxicants, but the list still does not match the other developed nations recommendations. Naturally, differences in patient characteristics between countries contribute to this, but the epidemiology of patients with poisoning and treatment infrastructure also change over time. A study examining changes in the frequency of poisoning from these 15 toxicants based on calls to the Japan Poison Information Center show changes over time for individual toxicants. Some toxicants, such as benzodiazepines and tricyclic acid, showed little variation but calls about bromovalerylurea decreased rapidly from 2000 onward. However, calls about diphenhydramine, which is not on the list of 15, have been increasing rapidly.<sup>8</sup> This



**Table 3.** Comparison of recommended toxicants for analysis

	Japan, 1999 <sup>†</sup>	Added in this survey	USA, 2003 <sup>‡</sup>	UK, 2014 <sup>§</sup>
Methanol	✓		✓	
Barbiturates	✓		✓	
Benzodiazepines	✓			
Bromovalerylurea	✓			
Tricyclic acid	✓			
Acetaminophen	✓		✓	✓
Salicylic acid	✓		✓	✓
Theophylline	✓		✓	✓
Organic phosphorus pesticides	✓			
Carbamate pesticides	✓			
Glufosinate	✓			
Paraquat	✓			✓
Arsenic	✓			
Cyanide	✓			
Methamphetamine	✓			
Caffeine		✓		
Ethanol		✓	✓	✓
Lithium		✓	✓	✓
Ethylene glycol		✓	✓	
Diphenhydramine		✓		
CO-Hb and Met-Hb			✓	✓
Valproate			✓	✓
Carbamazepine			✓	
Digoxin			✓	✓
Iron			✓	✓
Transferrin			✓	

Comparison of toxicants recommended for immediate analysis in institutions that provide treatment for acute poisoning. The definition of “immediate” is within 1 h in the USA and within 2 h in the UK.

CO-Hb, carboxyhemoglobin; Met-Hb, methemoglobin.

<sup>†</sup>Recommended by the Japanese Society for Clinical Toxicology in 1999.<sup>1</sup>

<sup>‡</sup>Recommended by the National Academy of Clinical Biochemistry Laboratory Medicine in 2003.<sup>6</sup>

<sup>§</sup>Recommended by The Association for Clinical Biochemistry and Laboratory Medicine in 2014.<sup>5</sup>

indicates that recommended toxicants should now be reconsidered.

## Differences between facilities

This study found that facilities throughout Japan lacked the infrastructure to measure blood concentrations of toxicants,

especially secondary emergency care facilities. In the comments on the questionnaire, responding facilities expressed several strong desires in three areas: (i) compensation for costs, (ii) greater availability of screening kits, (iii) consolidation and systematization of blood concentration measurement. These are clearly the voices of working medical doctors who are fully aware of the importance of care for poisoned patients but are unable to practice clinical toxicology as they should due to lack of necessary infrastructure at their facility.

In facilities not capable of quantitative testing, screening kits for drugs of abuse are just barely capable of carrying out qualitative testing but the facilities must cover the cost of this testing in full because health insurance does not compensate points for it. Respondents from some facilities stated that their facility limited use of screening kits or even that their facility did not accept poisoned patients altogether for financial reasons.

The fact cannot be overlooked that many emergency care facilities on the front line of clinical toxicology lack the infrastructure for toxicological analysis. Policies that enable facilities practicing emergency medicine to widely implement testing should be enacted alongside recommendations concerning toxicants for blood concentration measurement. Specific actions that will be necessary include development of affordable testing systems that allow emergency care facilities to undertake in-house urgent testing for toxicants, grants of insurance points for simple qualitative testing, and consolidation of specimens for testing.

## CONCLUSION

THIS STUDY INVESTIGATED the current state of infrastructure for measurement of the blood concentration of toxicants for clinical toxicology in Japan. The results indicate that infrastructure for blood concentration measurement is still lacking. Policies to create better clinical infrastructure at frontline medical facilities should be devised.

## ACKNOWLEDGMENTS

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## DISCLOSURE

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and conforms to the provisions of the Declaration of Helsinki. The Ethics

Committee of St. Luke's International Hospital approved the study (Approval No. 18-R095).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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